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# On the use of analytic expressions for the voltage distribution to analyze intracellular recordings.

*Note on “Characterization of subthreshold voltage fluctuations  
in neuronal membranes”*

**M. Rudolph and A. Destexhe**

Unité de Neurosciences Intégratives et Computationnelles, CNRS,  
91198 Gif-sur-Yvette, France.

Corresponding author:

Dr. A. Destexhe  
Unité de Neurosciences Intégratives et Computationnelles (UNIC), CNRS  
Bat. 32-33, 1 Avenue de la Terrasse  
91198 Gif-sur-Yvette  
France

Tel: 33-1-69-82-33-35  
Fax: 33-1-69-82-34-27  
e-mail: Destexhe@iaf.cnrs-gif.fr

## Abstract

Different analytic expressions for the membrane potential distribution of membranes subject to synaptic noise have been proposed, and can be very helpful to analyze experimental data. However, all of these expressions are either approximations or limit cases, and it is not clear how they compare, and which expression should be used in a given situation. In this note, we provide a comparison of the different approximations available, with an aim to delineate which expression is most suitable for analyzing experimental data.

Synaptic noise can be modeled by fluctuating conductances described by Ornstein-Uhlenbeck stochastic processes (Destexhe, Rudolph, Fellous, & Sejnowski, 2001). This system was investigated by using stochastic calculus to obtain analytic expressions for the steady-state membrane potential ( $V_m$ ) distribution (Rudolph & Destexhe, 2003; 2005). Analytic expressions can also be obtained for the moments of the underlying three-dimensional Fokker-Planck equation (FPE) (Richardson, 2004), or by considering this equation under different limit cases (Lindner & Longtin, 2006). One of the greatest promises of such analytic expressions is that they can be used to deduce the characteristics of conductance fluctuations from intracellular recordings *in vivo* (Rudolph et al., 2004; 2005).

A recent article (Lindner & Longtin, 2006) provided an in-depth analysis of some of these expressions, as well as different analytically-exact limit cases. One of the conclusions of this analysis was that the original expression provided by Rudolph & Destexhe (2003) was derived using steps that were incorrect for colored noise, and that the expression obtained matches numerical simulations only for restricted ranges of parameters. The latter conclusion was in agreement with the analysis provided in Rudolph & Destexhe (2005). Another conclusion was that the “extended expression” proposed by Rudolph & Destexhe (2005), although providing an excellent fit to  $V_m$  distributions in general, does not match for some parameter values and in particular, it does not agree with the analytically-exact static-noise limit. This extended expression is therefore not an exact solution of the system either. Since several analytic expressions were provided for the steady-state  $V_m$  distribution (Rudolph & Destexhe, 2003; Richardson, 2004; Rudolph & Destexhe, 2005; Lindner & Longtin, 2006), and since all of these expressions are either approximations or limit cases, it is not clear how they compare and which expression should be used in a given situation. In particular, it is unclear which expression should be used to analyze experimental recordings. In the present note, we attempt to answer these questions by clarifying a number of points about some of the previous expressions, and by providing a detailed comparison of the different expressions available in the literature.

First, we would like to clarify a number of misleading statements we made in the original article (Rudolph & Destexhe, 2003), and which may lead to confusion. The goal of this paper was to obtain an analytic expression for the steady-state  $V_m$  distribution of membranes subject to conductance-based colored noise sources. To obtain this, we considered the full system under a  $t \rightarrow \infty$  limit. In this limit, we noted that the noise time constants become infinitesimally small compared to the time over which the system is considered, and this property allowed us to treat the system as for white noise. Our

main assumption was that this procedure would allow us to obtain the correct steady-state properties like the  $V_m$  distribution. Our approach was to obtain a simplified FPE which gives the same steady-state solutions as the FPE describing the full system. These assumptions were stated in the Results of Rudolph & Destexhe (2003), but were not clearly stated in the Abstract and Discussion, and it could be understood that we claimed to provide an FPE valid for the full system. We clarify here that the treatment followed in that paper did not intend to describe the full system, but was only restricted to steady-state solutions.

Unlike the original expression (Rudolph & Destexhe, 2003), which matches only for a restricted range of parameters, the extended expression (Rudolph & Destexhe, 2005) matches for several orders of magnitude of the parameters (see also supplementary information of Rudolph & Destexhe, 2005). Why the extended expression matches so well, although it is not an exact solution of the system (Lindner & Longtin, 2006), is presently unknown. It is not due to the presence of boundary conditions, which could compensate for mismatches “by chance”. Simulations with and without boundary conditions gave equally good fits for the parameters considered here (see NEURON code in supplementary information). Our interpretation (Rudolph & Destexhe, 2005) is that the  $t \rightarrow \infty$  limit altered the spectral structure of the stochastic process (filtering), and one can recover a better spectral structure by following the same approximation for a system that is solvable (e.g., that of Richardson, 2004) and correct it accordingly. Thus, as also found by Lindner & Longtin (2006), the extended expression is a very good approximation of the steady-state  $V_m$  distribution. Other expressions have been proposed under different approximations (Richardson, 2004) or limit cases (Lindner & Longtin, 2006) and also match well the simulations for the applicable range of parameters.

Since different expressions were proposed corresponding to different approximations (Rudolph & Destexhe, 2003, 2005; Richardson, 2004; Lindner & Longtin, 2006), we investigated which expression must be used in practical situations. We have considered an extended range of parameters and tested all expressions by running the model for 10,000 randomly-selected values within this parameter space. The results of this procedure are shown in Fig. 1A-D. The smallest error between analytic expressions and numerical simulations was found for the extended expression of Rudolph & Destexhe (2005), followed by Gaussian approximations of the same authors and that of Richardson (2004). The fourth best approximation was the static-noise limit by Lindner & Longtin (2006). By scanning only within physiologically-relevant values based on conductance measurements in cats *in vivo* (Rudolph et al., 2005), the same ranking was observed (Fig. 1E), with even more drastic differences (up to 95%; see supplementary information). Manual examination of the different parameter sets where the extended expression was not the best estimate revealed that this happened when both time constants were slow (“slow synapses”; decay time constants  $>50$  ms). Indeed, performing parameter scans restricted to this region of parameters showed that the extended expression, while still providing good fits to the simulations, ranked first for less than 30% of the cases, while the static-noise limit was the best estimate for almost 50% of parameter sets (Fig. 1F; see details in supplementary information). Scanning parameters within a wider range of values including fast/slow synapses and weak/strong conductances showed that the extended expression was still the best estimate (about 47%), followed by the static-noise limit (37%; see supplementary information).

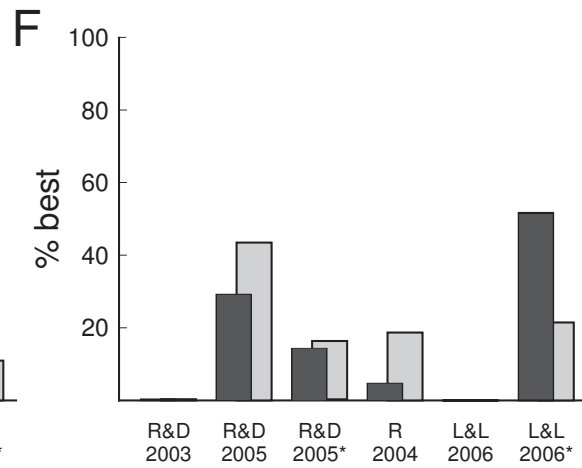
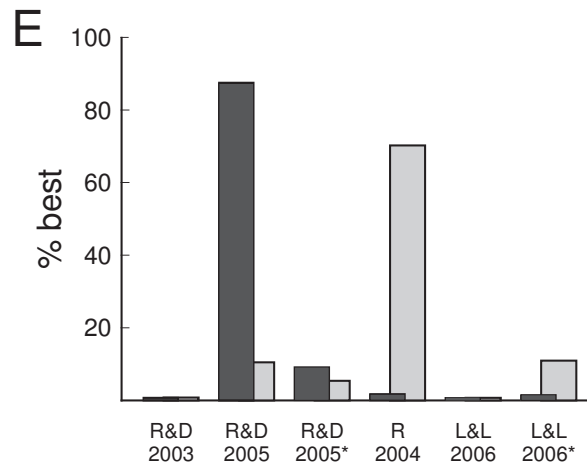
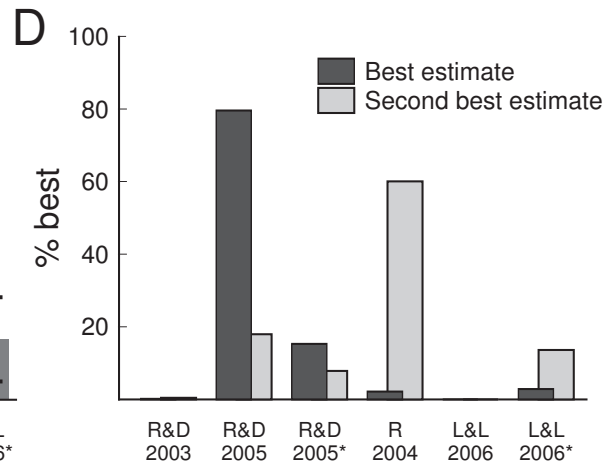
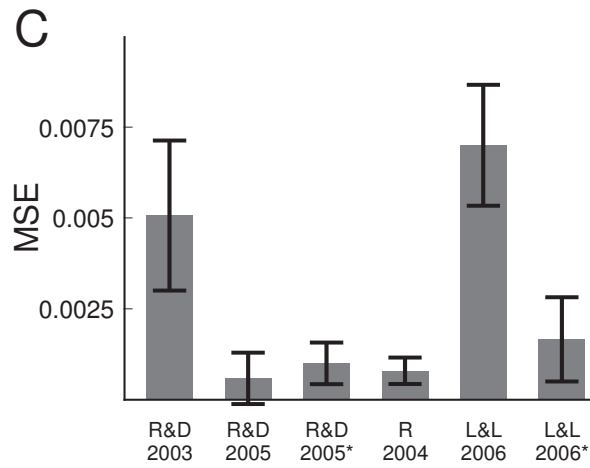
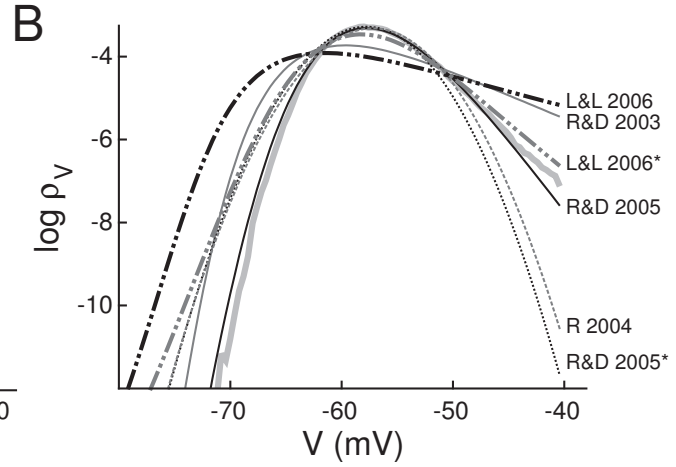
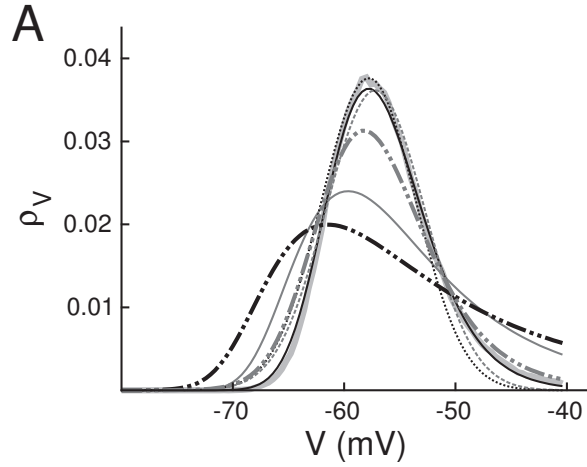
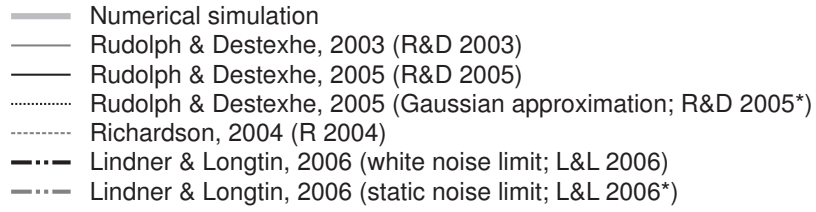
In conclusion, we have clarified here two main points. First, we clarified the assumptions and approximations that were too ambiguously stated in Rudolph & Destexhe (2003). Second, we provided a comparison of the different expressions available so far in the literature. This comparison showed that, for physiologically-relevant parameter values, the extended expression of Rudolph & Destexhe (2005) is the most accurate for about 80-90% of the cases. Outside of this range, however, the situation may be different. In systems driven by slow noisy synaptic activity, the static-noise limit performed better. We therefore conclude that, for practical situations of realistic conductance values and synaptic time constants, the extended expression provides the most accurate alternative available. This is also supported by the fact that the extended was successfully tested in real neurons (Rudolph et al., 2004), which is perhaps the strongest evidence that this approach provides a powerful tool to analyze intracellular recordings.

## Acknowledgments

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**Fig. 1:** Comparison of the accuracy of different analytic expressions for the  $V_m$  distributions of membranes subject to colored conductance noise. **A.** Example of  $V_m$  distribution calculated numerically (thick gray trace; model from Destexhe et al., 2001, simulated during 100 s), compared to different analytic expressions (see legend). **B.** Same as in A in log scale. **C.** Mean square error obtained for each expression by scanning a plausible parameter space spanned by 7 parameters. 10,000 runs similar to A were performed, using randomly-chosen (uniformly distributed) parameter values. For each run, the mean-square error was computed between the numerical solution and each expression. Parameters varied and range of values: membrane area  $a = 5,000$ – $50,000 \mu\text{m}^2$ , mean excitatory conductance  $g_{e0} = 10$ – $40 \text{ nS}$ , mean inhibitory conductance  $g_{i0} = 10$ – $100 \text{ nS}$ , correlation times  $\tau_e = 1$ – $20 \text{ ms}$  and  $\tau_i = 1$ – $50 \text{ ms}$ . The standard deviations ( $\sigma_e, \sigma_i$ ) were randomized between 20 and 33% of the mean conductance values, to limit the occurrence of negative conductances (in which case some analytic expressions would not apply). Fixed parameters: leak conductance density  $g_L = 0.0452 \text{ mS cm}^{-2}$  and reversal potential  $E_L = -80 \text{ mV}$ , specific membrane capacitance  $C_m = 1 \mu\text{F cm}^{-2}$ , and reversal potentials for excitation and inhibition:  $E_e = 0 \text{ mV}$  and  $E_i = -75 \text{ mV}$ , respectively. **D.** Histogram of best estimates (black) and second best estimates (gray; both expressed in % of the 10,000 runs in B). The extended expression (R&D 2005) had the smallest mean-square error for about 80% of the cases. The expression of Richardson (2004) was the second best estimate for about 60% of the cases. **E.** Similar scan of parameters restricted to physiological values (taken from Rudolph et al., 2005;  $g_{e0} = 1$ – $96 \text{ nS}$ ,  $g_{i0} = 20$ – $200 \text{ nS}$ ,  $\tau_e = 1$ – $5 \text{ ms}$  and  $\tau_i = 5$ – $20 \text{ ms}$ ). In this case, R&D 2005 was the most performant for about 86% of the cases. **F.** Scan using strong conductances and slow time constants ( $g_{e0}$  and  $g_{i0} = 50$ – $400 \text{ nS}$ ,  $\tau_e$  and  $\tau_i = 20$ – $50 \text{ ms}$ ). In this case, the static-noise limit L&L 2006\* was the most performant for about 50% of the cases. All simulations were performed using the NEURON simulation environment (Hines & Carnevale, 1997) See supplementary information for additional scans and the NEURON code of these simulations.

## Appendix with Supplementary Information

In this supplementary information, we provide more details about the comparison between different analytic expressions for the steady-state  $V_m$  distribution of neurons subject to conductance-based synaptic noise. These different approximations are respectively:

RD2003: Original analytic expression of Rudolph & Destexhe (2003);

RD2005: An “extended” analytic expression based on *RD2003*, where the time constants have been corrected to account for larger ranges of parameters (Rudolph & Destexhe, 2005);

RD2005\*: A Gaussian approximation of the extended expression *RD2005* (Rudolph & Destexhe, 2005);

R2004: An effective time constant approximation (Richardson, 2004), which is equivalent to a current-based approximation and is also Gaussian;

LL2006: An analytically-exact white-noise approximation (limit of time constants  $\rightarrow 0$ ; Lindner & Longtin, 2006);

LL2006\*: An analytically-exact static-noise approximation (limit of time constants  $\rightarrow \infty$ ; Lindner & Longtin, 2006).

Figure 1A-D of the paper shows a scan of 10,000 parameter values, randomly chosen within reasonable bounds (larger than physiological values). For each parameter set, 100 sec of activity was simulated and the  $V_m$  distribution was computed numerically. This numerical estimate was then compared to each of the six expressions outlined above. In this scan, *RD2005* was the best estimate in about 80 % of the cases, while the second-best estimate was *R2004* in about 60 % of the cases.

## Additional analyses and scans of parameters

In this supplementary information, we provide more examples of parameter scans (using the same procedure as described in the paper), as well as illustrate some typical situations. As a first example, we scanned 10,000 parameter sets within strictly “physiological” values. Those values were obtained from a recent study (Rudolph et al., 2005), in which the synaptic noise was analyzed from intracellular recordings of neurons in cat parietal cortex *in vivo*. This analysis used both classic conductance analysis methods, the extended expression *RD2005*, as well as direct matching of compartmental models to the recordings (see details in Rudolph et al., 2005). Both up/down states (Ketamine-Xylazine anesthesia) and EEG-activated states were used for the analysis (n=12 cells). The minimal and maximal values for the conductances and variances obtained in those measurements were used as bounds for choosing the 10,000 parameters. The results of these simulations are shown in Fig. S-1A. Similar to Fig. 1, *RD2005* was the most accurate estimate for about 86 % of the cases, followed by the *R2004* approximation. Because including two expressions biases the analysis against *RD2005*, we also repeated the same analysis by removing the Gaussian approximation *RD2005\**, as shown in Fig. S-1B. In this case, *RD2005* was the best estimate for about 95% of the parameter sets.

Manual examination of the cases for which *RD2005* was not the best estimate revealed that this happened when both time constants were slow (“slow synapses”; decay time constants  $>50$  ms). An example of such

distribution is shown in Fig. S-2. In this case, the static-noise limit *LL2006\** was the best estimate, followed by *RD2005*.

To explore this region of parameters, we performed two additional runs of 5,000 randomly selected values of parameters, contrasting a region of parameter with fast time constants with the same region with slow time constants. When time constants were fast, *RD2005*, *RD2005\** and *M2004* accounted for the best performance (Fig. S-3A), in agreement with above. However, for slow time constants, the most accurate estimate was obtained by using the static noise limit (Fig. S-3B; identical run as Fig. 1F of the paper). The performance of static noise limit is not surprising since this expression is specific for systems with infinitely large noise time constants.

A last run was realized using a wider parameter range (Fig. S-4), that included physiological values, as well as slow synapses and strong conductances. The parameter space scanned included all regions of parameters scanned in all preceding runs. Based on a set of 10,000 parameter values randomly chosen within this parameter space, the *RD2005* expression still provided the largest number of best estimates (about 50% of the cases), followed by the static-noise limit *LL2006\** (37%). Similar values were obtained by removing *RD2005\** from the analysis (Fig. S-4B).

Based on these runs, we conclude that, for physiologically-relevant parameter values, the extended expression *RD2005* is the most accurate for about 80-90% of the cases. Outside of this range, however, the situation is different. The static noise limit can be a better approximation for systems with large noise time constants (“slow synapses”), and should be used in such cases.

## NEURON Code

All simulations above and in the paper were done under the NEURON simulation environment (Hines & Carnevale, 1997). The NEURON source code that was used for the simulations shown here, as well as the code for data analysis and drawings, can be found at the following location:

[http://cns.iaf.cnrs-gif.fr/files/Note2006\\_demo.zip](http://cns.iaf.cnrs-gif.fr/files/Note2006_demo.zip)

This code contains two parts. First, a scanning program runs the numeric simulations for the 10,000 parameters, and writes the results to a data file. Second, an analysis/drawing program reads this data file and creates the histograms shown in Fig. 1. The user can easily change the parameters and verify the simulations shown here, or perform scans in unexplored parameter ranges, and thereby contribute to a more rich analysis of how the different analytic expressions fit numeric simulations.

Note that, contrary to the previous papers (Rudolph & Destexhe, 2003, 2005), no boundary conditions were used here, and the codes provided allow the conductance to go negative. Similar results were obtained when boundary conditions were used (this is easy to modify in the code provided).

## Experimental tests and analysis of experimental data

Finally, another test of the analytic expressions is by comparing them directly to experimental data. The *RD2005* expression is the basis of a recently proposed method to analyze intracellular recordings by fitting experimental distributions, yielding estimates of parameters of the real synaptic noise, such as the mean and variance of



excitatory and inhibitory conductances (Rudolph et al., 2004). This method is presently used by several laboratories around the world. Related to the present paper, the *RD2005* expression was tested against experimental data, in different ways. First, the conductances obtained by using the *RD2005*-based method were compared to other methods for conductance analysis, as well as to the direct matching of computational models to experimental data. These different methods yielded consistent results for activated states recorded intracellularly in cat parietal cortex *in vivo* (see Rudolph et al., 2005), suggesting that *RD2005* is accurate for the parameters corresponding to this type of synaptic noise in cortical neurons *in vivo* (indeed those are the parameters shown in Fig. S-1).

A second test, more severe, was realized using the dynamic-clamp technique. The synaptic noise produced spontaneously in ferret cortical slices (“up-states”) was analyzed using *RD2005*, yielding estimates of the conductance parameters. An artificial synaptic noise was then generated using the estimated parameters, and was re-injected in the *same neuron* during quiescent activity using dynamic-clamp. This yields a “recreated” state that can be compared to the “natural” state. This procedure was successful, as shown by the matching of the natural and artificial  $V_m$  distributions (see Fig. 7 and Fig. 8A in Rudolph et al., 2004). Another test, equally severe, was to first inject synaptic noise with known parameters, and then compare the  $V_m$  distribution obtained in the real neuron with the analytic prediction of *RD2005*. This procedure also yielded consistent estimates (Fig. 8B in Rudolph et al., 2004).

These experiments and analyses show that the extended expression *RD2005* can provide a very useful analysis tool for extracting conductances from experimental data, and that the accuracy of this analysis is acceptable. Other expressions could possibly be used in similar paradigms, but this has not been done yet. Future experiments should be designed to address the respective accuracy of the different expressions using similar procedures, which would constitute a further test of their respective accuracy in physiological conditions.

## Resources

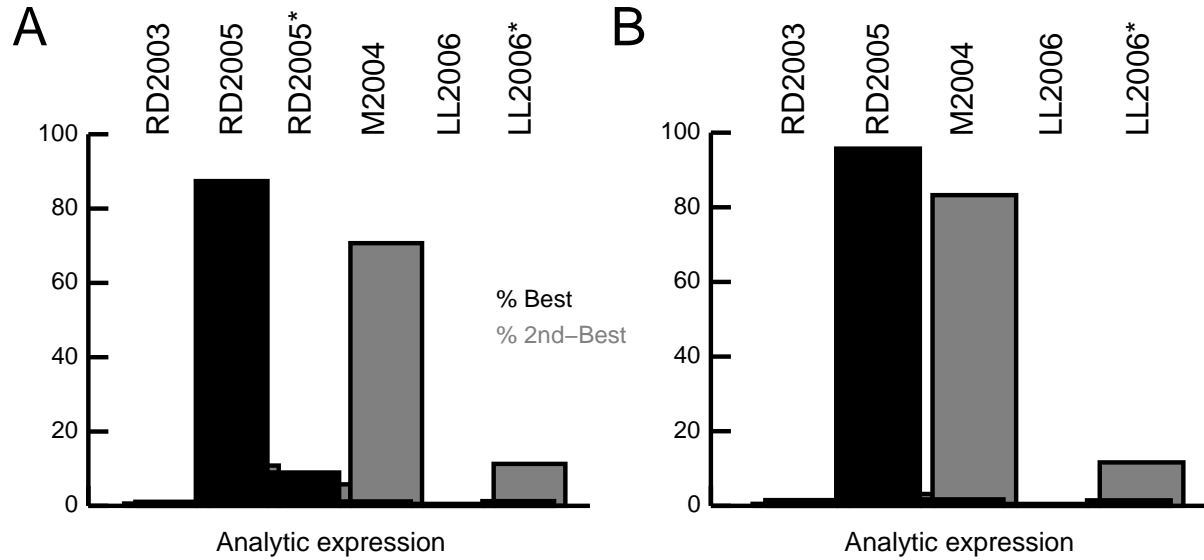
Electronic (PDF) copies of the paper and supplementary information are available at:

<http://cns.iaf.cnrs-gif.fr/files/Note2006.pdf>

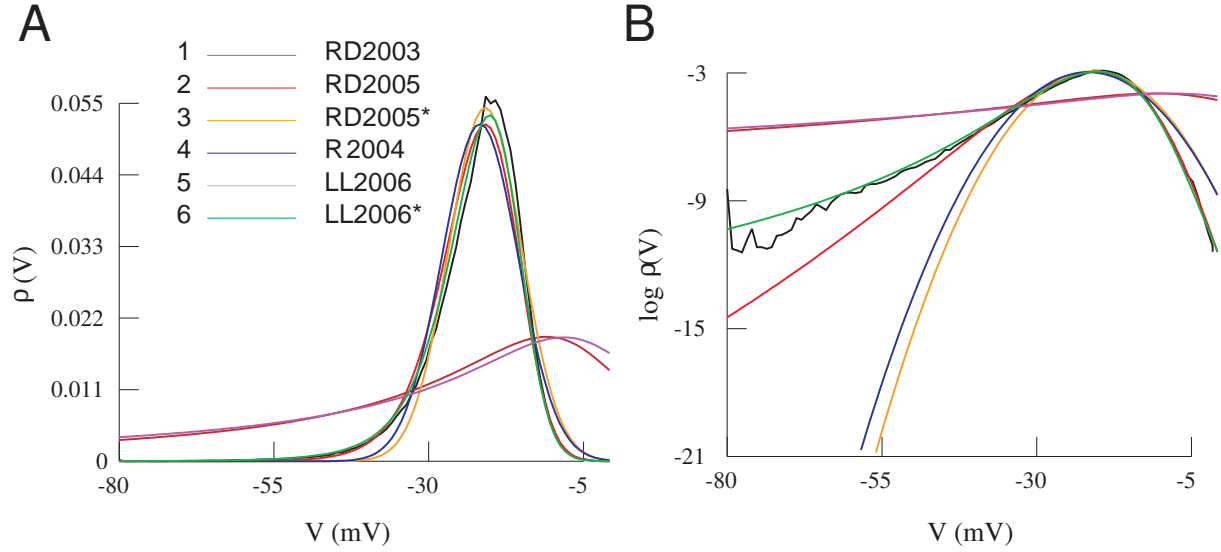
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The NEURON code corresponding to the simulations is available at:

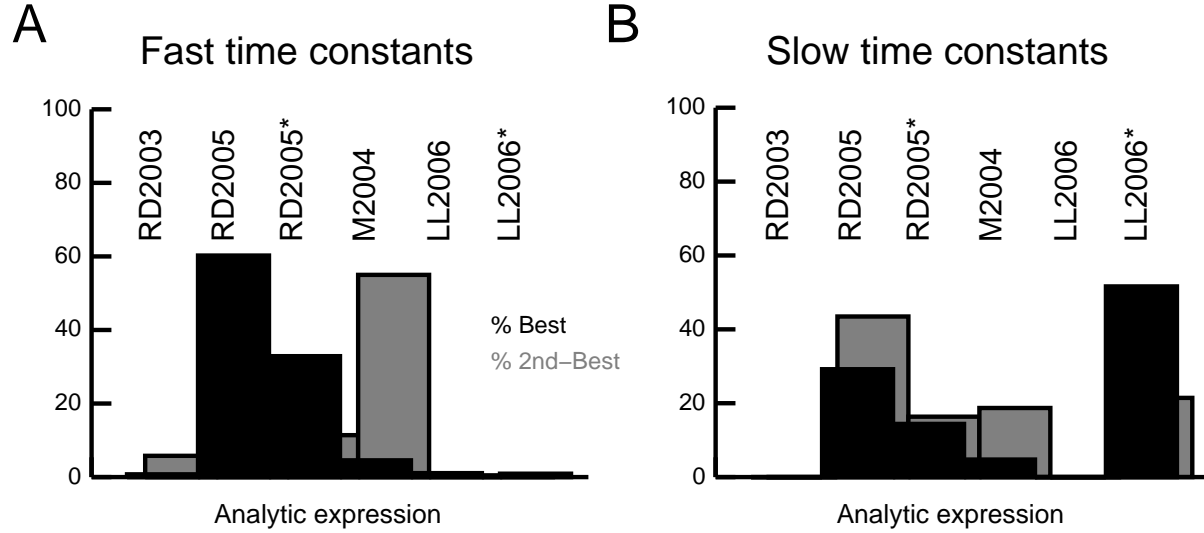
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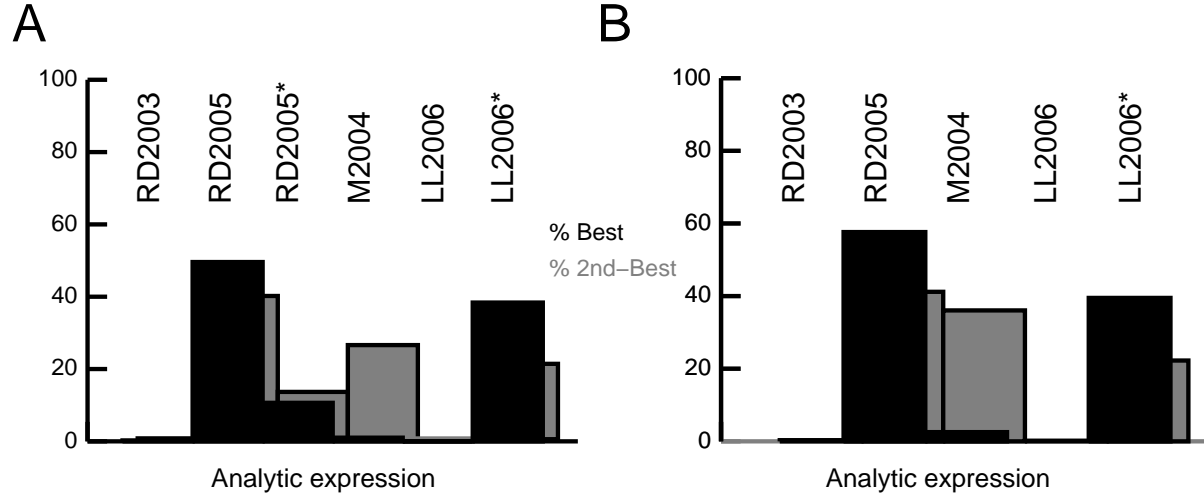
**Fig. S-1:** Histogram of best estimates for physiological values of parameters. **A.** Additional scan of 10,000 runs of parameters using randomly-chosen parameter (same procedure as in Fig. 1 of the accompanying article) within the following range: membrane area  $a = 5,000\text{--}50,000 \mu\text{m}^2$ , mean excitatory conductance  $g_{e0} = 1\text{--}96 \text{ nS}$ , mean inhibitory conductance  $g_{i0} = 20\text{--}200 \text{ nS}$ , correlation times  $\tau_e = 1\text{--}5 \text{ ms}$  and  $\tau_i = 5\text{--}20 \text{ ms}$ . The red dashed histograms show the second best estimates. The extended expression (*RD2005*) had the smallest mean-square error for about 86% of the cases. **B.** Same set of simulations, but the histogram was calculated by removing *RD2005\**. In this case, *RD2005* was the most accurate for about 95% of the cases.



**Fig. S-2:** Example of  $V_m$  distribution for parameters where the static noise limit is the best approximation. The  $V_m$  distributions are shown using a similar layout as Fig. 1A-B of the accompanying article (left: linear scale, right: log-scale; color code in inset). The best fit was in this case the static noise limit (*LL2006\**, green), while *RD2005* was second best (red). Parameters: membrane area  $a = 37286 \mu\text{m}^2$ , excitatory conductance  $g_{e0} = 400 \text{ nS}$ ,  $\sigma_e = 130 \text{ nS}$ , mean inhibitory conductance  $g_{i0} = 141 \text{ nS}$ ,  $\sigma_i = 39 \text{ nS}$ , correlation times  $\tau_e = 35.4 \text{ ms}$  and  $\tau_i = 20.8 \text{ ms}$ .



**Fig. S-3:** Histogram of best estimates for fast and slow time constants. Two additional scans of 5,000 parameters each are shown in **A** and **B**, using the same procedure as in Fig. 1 of the accompanying article. The same parameters were used in both scans ( $a = 5,000\text{--}50,000 \mu\text{m}^2$ ;  $g_{e0} = 1\text{--}50 \text{ nS}$ ,  $g_{i0} = 1\text{--}50 \text{ nS}$ ), except for the time constants ( $\tau_e = 1\text{--}5 \text{ ms}$  and  $\tau_i = 5\text{--}20 \text{ ms}$  in **A**;  $\tau_e$  and  $\tau_i = 50\text{--}200 \text{ ms}$  in **B**). The red dashed histograms show the second best estimates. For fast time constants, *RD2005* was the most accurate estimate for about 60% of the cases, whereas for slow time constants, *LL2006\** was more accurate for about 50% of the runs.



**Fig. S-4:** Histogram of best estimates for scans within a wide range of parameter values. **A.** Additional scan of 10,000 runs of parameters using randomly-chosen parameters (same procedure as in Fig. 1 of the accompanying article) within the following range:  $a = 1,000\text{--}100,000 \mu\text{m}^2$ ,  $g_{e0} = 1\text{--}300 \text{ nS}$ ,  $g_{i0} = 1\text{--}300 \text{ nS}$ ,  $\tau_e = 1\text{--}200 \text{ ms}$  and  $\tau_i = 1\text{--}200 \text{ ms}$ . The red dashed histograms show the second best estimates. The extended expression (*RD2005*) had smallest mean-square error for about 50% of the cases. **B.** Same set of simulations, but the histograms were calculated by removing *RD2005\**. In this case, *RD2005* was the most performant for about 57% of the cases.